Clindamycin Phosphate 1.2%/ Tretinoin 0.025% Gel for the Treatment of Acne Vulgaris: Which Patients are Most Likely to Benefit the Most?

JAMES Q. DEL ROSSO, DO, FAOCD
Las Vegas Dermatology, Las Vegas, Nevada; Touro University College of Osteopathic Medicine, Henderson, Nevada

ABSTRACT

Clindamycin phosphate 1.2%/tretinoin 0.025% gel is a topical combination formulation used once daily for the treatment of acne vulgaris, with approval in the United States for patients >12 years of age. Three 12-week, randomized, vehicle-controlled, pivotal trials included >1,800 actively treated subjects. In addition, an open-label, 52-week study was also completed with 442 subjects enrolled. The skin tolerability, safety, and efficacy of clindamycin phosphate 1.2%/tretinoin 0.025% gel applied once daily is well-established based on data from pivotal studies and analyses in other subsequent publications including from pooled analysis of results from 4,550 subjects. This article discusses results from the pivotal 12-week, Phase 3 studies of clindamycin phosphate 1.2%/tretinoin 0.025% gel applied once daily in 845 subjects with mild, moderate, or severe facial acne vulgaris and differentiates patterns of therapeutic response using study endpoint successes defined as clear, almost clear, or at least a 2-grade improvement in the AV severity rating.
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Clindamycin phosphate 1.2%/tretinoin 0.025% gel (ClinP/Tret; Ziana gel, Valeant Pharmaceuticals) is a combination topical formulation that was approved by the United States Food and Drug Administration (FDA) in 2006 and is indicated for "the topical treatment of acne vulgaris in patients 12 years or older".[1] Study enrollment included subjects with facial acne vulgaris (AV) who were graded as mild, moderate, or severe based on criteria specified in the study protocol.[1,2] FDA approval included evaluation of three prospective, multicenter, randomized controlled trials (RCTs). Two of these pivotal trials followed identical study protocols, with comparison of ClinP/Tret gel versus each of the individual active ingredients and vehicle. In these two pivotal RCTs, ClinP/Tret gel (n=845) applied once daily proved to be superior in efficacy to tretinoin 0.025% (n=846), clindamycin phosphate 1.2% (n=426), and vehicle (n=423) and also demonstrated favorable skin tolerability and safety in subjects with facial AV graded as mild, moderate, or severe.[1,2] In the third RCT, ClinP/Tret gel (n=1008) proved to be superior to clindamycin phosphate 1.2% (n=1002) in efficacy, with favorable skin tolerability and safety also reconfirmed, in subjects with facial AV graded as moderate or severe.[1,2]

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ADDRESS CORRESPONDENCE TO: James Q. Del Rosso, DO; E-mail: jqdelrosso@yahoo.com

TABLE 1. Patient demographics: Comparison of total patient population and those clear/almost clear by Week 12 (ITT population, pooled data pivotal Phase 3 studies)

	OVERALL (N=845)	WEEK 12 (N=185)
AGE (mean)	19.0	20.4
GENDER (N, %)		
Male	412 (48.8%)	78 (42.1%)
Female	433 (51.2%)	107 (57.9%)
ETHNICITY		
Hispanic/Latino (N, %)	102 (12.1%)	24 (13.0%)
RACE		
Caucasian (N, %)	616 (72.9%)	130 (70.3%)
SEVERITY (N, %)		
Mild	118 (14.0%)	37 (20.0%)
Moderate	605 (71.6%)	135 (73.0%)
Severe	119 (14.1%)	12 (6.5%)
Very severe	1 (0.1%)	1 (0.5%)
Not reported	2	0
Mean inflammatory lesions	29.5	27.5
Mean noninflammatory lesions	48.6	40.9
Mean total lesions	78.1	68.3

In addition to the published data from the pivotal RCTs, additional research has demonstrated other clinically relevant findings related to the use of ClinP/Tret gel for treatment of facial AV. ClinP/Tret gel has been used effectively in combination with a benzoyl peroxide cloth formulation, an observation that is important due to concerns related to emergence of clindamycin-resistant strains of *Propionibacterium acnes*.[3] A RCT study (N=33) in subjects ≥12 years of age with Fitzpatrick skin type IV to VI demonstrated that ClinP/Tret gel applied once daily was effective and well-tolerated for treatment of facial AV of mild to moderate severity in patients with skin of color (dark skin).[4] A randomized, evaluator-blinded, split-face, 21-day study reported that ClinP/Tret gel (n=45) was better tolerated than tretinoin microsphere gel 0.1% (n=23), with outcomes demonstrating significantly reduced erythema (P<0.04), scaling (P<0.03), itching (P<0.02), burning (P<0.03), and stinging (P<0.04) with use of ClinP/Tret gel; trends for greater erythema, scaling, and subjective discomfort for 0.1% adapalene gel as compared to ClinP/Tret gel were noted, however, these differences were not statistically significant.[5] Lastly, following designated protocols for irradiation with ultraviolet (UV) light exposure (UVA, UVB) and visible light, ClinP/Tret gel demonstrated a low potential for phototoxicity (n=37) and photoallergenicity (n=58).[6]

This article evaluates results from Phase 3 RCTs of ClinP/Tret gel applied once daily for 12 weeks in 845 study subjects with mild, moderate, or sever facial AV. The objective of this analysis is to differentiate patterns of therapeutic response using *study endpoint successes* (often referred to as treatment success in clinical trials) defined in the study protocol as clear, almost clear, or at least a 2-grade improvement in AV severity rating.

METHODS

A *post hoc* analysis of pivotal Phase 3 studies inclusive of 845 subjects with mild, moderate, or severe facial AV treated with ClinP/Tret gel once daily for 12 weeks was completed. The subjects were ≥12 years of age. Demographic information and data related to parameters of AV at baseline were compared for those subjects who were study endpoint successes, described as clear, almost clear, or at least a 2-grade improvement in grading of AV severity at Week 12.

DEMOGRAPHIC DATA AND BASELINE DATA OF ACNE VULGARIS PARAMETERS

The majority of enrolled subjects in the analyzed Phase 3 studies at baseline were of white skin (72.9%), with a mean age of 19 years, essentially equal in gender distribution. In addition, the majority of subjects were graded as moderate severity AV at baseline (71.6%). The distribution was relatively equal at baseline among subjects graded as mild AV (14.0%) and severe AV (14.1%). Demographic data and parameters of AV at baseline (i.e., severity grading, lesion counts) are depicted in the "Overall" column in Table 1, inclusive of 845 subjects who were actively treated with ClinP/Tret gel once daily.

RESULTS OF DATA ANALYSIS

Table 1 depicts the demographic data and parameters of AV of enrolled subjects treated with ClinP/Tret gel once daily at baseline (n=845) and the same information only for subjects who achieved the study endpoint successes of clear or almost clear AV severity rating after 12 weeks of treatment (n=185). Further analysis of demographic information showed a higher proportion of female patients (n=107, 57.9%) among the subset of subjects who achieved study endpoint success. Overall, 24.7 percent of female subjects and 18.9 percent of male subjects in the two studies achieved study endpoint success. Assessment of parameters of AV also showed that patients with mild or moderate AV were more likely to achieve study endpoint success as compared to subjects with severe AV. This

TABLE 2. Patient demographics: Those clear/almost clear by study visit (ITT population pooled data, pivotal Phase 3 studies)

	BASELINE (N=845)	WEEK 2 (N=18)	WEEK 4 (N=45)	WEEK 8 (N=102)	WEEK 12 (N=185)
AGE (mean)	19.0	17.8	22.0	21.6	20.4
GENDER					
Male (%)	48.8%	33.3%	35.6%	39.2%	42.1%
Female (%)	51.2%	66.7%	64.4%	60.8%	57.9%
ETHNICITY					
Hispanic/Latino (%)	12.1%	5.6%	13.3%	11.8%	13.0%
RACE					
Caucasian (%)	72.9%	83.3%	68.9%	68.6%	70.3%
SEVERITY					
Mild (%)	14.0%	27.8%	45.0%	24.5%	20.0%
Moderate (%)	71.6%	72.2%	55.0%	72.5%	73.0%
Severe (%)	14.1%	0%	0%	3.0%	6.5%
Very severe (%)	0.1%	0%	0%	0%	0.5%
Mean inflammatory lesions	29.5	25.8	27.0	26.2	27.5
Mean noninflammatory lesions	48.6	46.6	38.4	39.4	40.9
Mean total lesions	78.1	72.4	65.4	65.6	68.3

latter observation was intuitively anticipated, especially as severe AV is not typically treated with topical therapy alone.

Table 2 shows the demographic information and data on AV parameters of those subjects who achieved study endpoint success after two weeks (n=18), four weeks (n=45), eight weeks (n=102), and 12 weeks (n=185). In the early weeks of the study, including the first follow-up visit after enrollment (Week 2), those patients who obtained study endpoint success tended to be younger, with a mean age of 17.8 years. To add, approximately two-thirds of subjects achieving study endpoint success were female (66.7%). The apparent high magnitude of therapeutic benefit seen overall among female subjects was maintained over the 12-week duration (study endpoint). Achievement of study endpoint success was observed in some subjects early in the course of the study who presented with mild AV or moderate AV at baseline; however, study endpoint success was not observed until after eight weeks in subjects who exhibited severe AV at baseline.

CONCLUSIONS AND DISCUSSION

The safety and efficacy of ClinP/Tret gel applied once daily in the treatment of facial AV is well-established, based on pivotal RCTs and other subsequent publications.[1] This analysis evaluates data from subjects treated with ClinP/Tret gel who were enrolled in two Phase 3, 12-week RCTs that followed an identical study protocol. Subjects who were actively treated with ClinP/Tret gel and achieved *study endpoint successes* as defined in the protocol were included for analysis. Assessment of the data appear to identify those patients with AV most likely to achieve substantial therapeutic benefit from once-daily

treatment with ClinP/Tret gel over the first 12 weeks. Although both genders demonstrated good efficacy and safety, female patients with AV and those with mild-to-moderate AV appear to respond more favorably to treatment with ClinP/Tret gel. There has been increased interest in possible gender differences related to treatment outcomes for AV. A *post hoc* analysis of dapsone-treated acne patients showed greater absolute efficacy in female subjects, although the mean treatment difference (active minus vehicle) was greater in male subjects.[7] A recent study with clindamycin-benzoyl peroxide (BP) 3.75% gel favored female acne patients both in terms of absolute efficacy and mean treatment difference.[8] Not surprisingly, patients with severe AV are less likely and slower to achieve a clear or almost clear study endpoint within 12 weeks. However, a visible therapeutic response (i.e., AV lesion reduction) can be observed in many patients and may be perceived as "real-world treatment success" by the patient and/or the clinician, as opposed to how treatment success is strictly defined in a RCT.

Another interesting observation for RCTs with use of ClinP/Tret gel once daily relates to the negligible risk of initial flaring of AV after initiation of therapy. Evaluation of subjects included in the three pivotal RCTs at two weeks after initiation of therapy demonstrated that ClinP/Tret gel was not associated with initial flaring of facial AV in subjects with AV severity ratings of mild, moderate, or severe at baseline.[9] The definitions of initial flaring used in this data analysis included capturing the percentage of subjects with a >10-percent increase in inflammatory AV lesions and the percentage of subjects with >20-percent increase in inflammatory lesions, both as compared to baseline. Interestingly, this same analysis showed that application of tretinoin 0.025% gel once daily as monotherapy was associated with initial flaring in some subjects with mild AV at baseline, and that ClinP/Tret gel exhibited the lowest percentage of any increase in inflammatory AV lesions after the first two weeks of treatment as compared to baseline.[9]

A long-term, multicenter, open-label, safety evaluation of ClinP/Tret gel applied once daily in subjects with mild (49%), moderate (38%), or severe (13%) facial AV at baseline was completed in one cohort over six months (n=442) and a second cohort over 12 months (n=213).[10] ClinP/Tret gel was well-tolerated, with 92, 91, and 94 percent of subjects reporting no itching, burning, or stinging, respectively; contact dermatitis and application-site reactions were reported in one percent of subjects. Overall, the efficacy of ClinP/Tret gel was sustained over the long-term duration of the study in the majority of subjects.[10]

The results of this analysis, along with pivotal RCTs and other additional studies support the efficacy and safety for treatment of AV. Three Phase 3, 12-week RCTs encompassed more than 1,800 subjects actively treated with ClinP/Tret gel, and an open-label, 52-week study included 442 enrolled subjects.[1,2,10] A recent pooled analysis (N=4,550) of subjects treated with ClinP/Tret gel demonstrated that the percentage reduction in inflammatory, noninflammatory, and total lesions, and success rate based on investigator global assessment (IGA), were significantly greater as compared with clindamycin alone, tretinoin alone, and vehicle alone (all $P<0.01$).[11] In this same report, subgroup analyses showed that the percentage reduction in all AV lesion types was significantly greater with ClinP/Tret gel in the adolescent subgroup (n=2915, $P<0.002$), and in subjects with mild AV or moderate AV (n=3662, $P<0.02$) versus comparators.[11] Importantly, in subjects with severe AV (n=880), the percentage reduction in all lesion types was significantly greater with ClinP/Tret gel versus vehicle ($P<0.0001$). Overall, a greater proportion of subjects treated with ClinP/Tret gel exhibited a ≥50 or ≥80-percent continuous reduction in all types of AV lesions at Week 12 compared with clindamycin, tretinoin and vehicle. Similar adverse event frequencies were noted in the active and vehicle groups, with baseline-adjusted mean tolerability scores over time reported as mild and similar in all study groups.[11]

As stated above, the RCTs submitted to the FDA during formal evaluation for approval evaluated the use of ClinP/Tret gel alone in subjects ≥12 years of age with facial AV.[1,2] However, combinations with topical and/or systemic therapies are often utilized in clinical practice, as an optimal approach incorporates multiple therapeutic agents that address different pathogenic factors of AV. This combination approach is recommended in multiple publications, including published treatment guidelines for AV.[3,12–14] The favorable skin tolerability profile of ClinP/Tret gel is beneficial when combining different topical therapies and formulations in a given patient, as cutaneous irritation is an adverse factor that can reduce adherence and prevent a successful therapeutic outcome.

REFERENCES

1. Prescribing Information, Ziana (clindamycin phosphate 1.2%/tretinoin 0.025%) gel, Valeant Pharmaceuticals (Medicis). www.ziana.com. Accessed on January 4, 2015.
2. Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol*. 2007;6:607–615.
3. Zeichner JA, Wong V, Linkner RV, Haddican M. Efficacy and safety of tretinoin 0.025%/clindamycin phosphate 1.2% gel in combination with benzoyl peroxide 6% cleansing cloths for the treatment of facial acne vulgaris. *J Drugs Dermatol*. 2013;12:277–282.
4. Callender VD, Young CM, Kindred C, Taylor SC. Efficacy and safety of clindamycin phosphate 1.2% and tretinoin 0.025% gel for the treatment of acne and acne-induced post-inflammatory hyperpigmentation in patients with skin of color. *J Clin Aesthet Dermatol*. 2012;5:25–32.
5. Leyden J, Wortzman M, Baldwin EK. Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and

adapalene gel. *J Drugs Dermatol*. 2009;8:383–388.
6. Murray J, Potts A. The phototoxic and photoallergy potential of clindamycin phosphate 1.2%/ tretinoin 0.025% gel for facial acne: results of two single-center, evaluator-blinded, randomized, vehicle-controlled Phase 1 studies in healthy volunteers. *J Drugs Dermatol*. 2014;13:16–22.
7. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs. male patients with facial acne vulgaris: gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2012;11:1417–1421.
8. Harper JC. The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in patients with facial acne vulgaris: gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2015;14:381–384.
9. Leyden JJ, Wortzman M. A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring. *Cutis*. 2008;82:151–156.
10. Kircik LH, Peredo MI, Bucko AD, et al. Safety of a novel gel formulation of clindamycin phosphate 1.2%-tretinoin 0.025%: results from a 52-week open-label study. *Cutis*. 2008;82:358–366.
11. Dréno B, Bettoli V, Ochsendorf F, et al. Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, Phase III studies. *Eur J Dermatol*. 2014;24:201–209.
12. Nast A, Dréno B, Bettoli V, et al. European evidence-based guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol*. 2012;26 Suppl 1:1–29.
13. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from the global alliance to improve outcomes in acne. *J Am Acad Dermatol*. 2003;49(suppl 1):S1–S38.
14. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2003;49(suppl 3):S200–S210.